(2)

(19)日本国特許庁（ＪＰ）　(12)**公表特許公報**（Ａ）　(11)特許出願公表番号

特表平8－505841

(43)公表日　平成８年(1996)６月25日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ
Ａ６１Ｋ　9/14			
47/30		Ｌ　7433－4Ｃ	
47/44		Ｌ　7433－4Ｃ	
		9455－4Ｃ	Ａ６１Ｋ　9／14　　Ａ

審査請求　有　　予備審査請求　有　　(全 22 頁)

(21)出願番号　特願平6－513413
(86)(22)出願日　平成５年(1993)11月26日
(85)翻訳文提出日　平成７年(1995)５月29日
(86)国際出願番号　ＰＣＴ／ＵＳ９３／１１５１７
(87)国際公開番号　ＷＯ９４／１２１５７
(87)国際公開日　平成６年(1994)６月９日
(31)優先権主張番号　０７／９８２，９７１
(32)優先日　1992年11月30日
(33)優先権主張国　米国（ＵＳ）
(81)指定国　ＥＰ(ＡＴ，ＢＥ，ＣＨ，ＤＥ，ＤＫ，ＥＳ，ＦＲ，ＧＢ，ＧＲ，ＩＥ，ＩＴ，ＬＵ，ＭＣ，ＮＬ，ＰＴ，ＳＥ)，ＡＵ，ＣＡ，ＪＰ，ＫＲ，ＮＺ

(71)出願人　ケーヴィ　ファーマセチカル　カンパニー
アメリカ合衆国，ミズーリー州　63144－2555　セントルイス，サウス　ハンリー　ロード　2503
(72)発明者　キューカ，ロバート　シー.
アメリカ合衆国，イリノイ州　62025　エドワーズヴィル，エドワーズ　ドライヴ　311
(72)発明者　ハーランド，ロナルド　スコット
アメリカ合衆国，モンタナ州　62017　チェスターフィールド，スケットラー　ヴァリー　ドライヴ　1944
(74)代理人　弁理士　萼　経夫　（外１名）

最終頁に続く

(54)【発明の名称】　味を隠された医薬材料

(57)【要約】
ａ）有効物質；ならびにｂ）（ｉ）約５０℃ないし約２００℃の範囲内の融点を有するワックスコア材；および（ii）局部疏水ポリマー材からなる空間的に配向されたマトリックスよりなる実質的に味のない医薬デリバリーシステム、ならびに同時にそれを作る方法。

【特許請求の範囲】

１．ａ）有効物質；ならびに

ｂ）（ｉ）より多量である１０－９５％量の約５０℃ないし約２００℃の範囲内の融点を有するワックスコア材；および（ii）より少量である５０％未満量の疏水性ポリマー材を含む空間的に配向されたマトリックスよりなる、実質的に味のない医薬デリバリーシステム（pharmacetical delivery system）。

２．上記有効物質が医薬品である請求項１に記載のデリバリーシステム。

３．上記有効物質が、鎮痛薬、抗炎症薬、抗ヒスタミン薬、鎮咳薬、去痰薬、うっ血除去薬、麻酔薬、抗生物質、気管支収縮薬、心臓血管薬、中枢神経系薬、無機塩、ビタミン、金属塩およびそれらの混合物からなる群から選択される、請求項１に記載のデリバリーシステム。

４．上記ワックスコア材がマトリックスの重量に対して約１０％ないし約９５％の量で存在する請求項１に記載のデリバリーシステム。

５．上記ワックスコア材がマトリックスの重量に対して約１５％ないし約８５％の量で存在する請求項１に記載のデリバリーシステム。

６．上記ワックスコア材が、１２ないし３２個の炭素原子を有する直鎖もしくは分枝鎖のアルキル基の長鎖脂肪炭化水素、エステル、酸およびアルコールから選択される、請求項１に記載のデリバリーシステム。

７．上記ワックスコア材が動物性ワックス、植物性ワックス、石油ワックス、合成ワックス、およびそれらの混合物からなる群から選択される請求項６に記載のデリバリーシステム。

８．上記ワックスコア材が蜜蝋、ラノリン、ステアリン酸、カンデリラワックス、カルナバワックス、微結晶性ワックス、カルボワックスおよびそれらの混合物から選択される請求項７に記載のデリバリーシステム。

９．上記疏水性ポリマー材がマトリックスの重量に対して約１％ないし約５０％の量で存在する請求項１に記載のデリバリーシステム。

１０．上記疏水性ポリマー材がマトリックスの重量に対して約３％ないし約１０％の量で存在する請求項１に記載のデリバリーシステム。

１１．上記疏水性ポリマー材が天然ポリマーまたは合成ポリマーである、請求項１に記載のデリバリーシステム。

１２．上記天然ポリマーが、セルロース、セルロースアセテート、セルロースフタレート、メチルセルロース、エチルセルロース、ゼイン、医薬用グレーズ、シェラック、キタン（chitan）、ペクチン、ポリペプチド類、それらの酸および塩基付加塩、およびそれらの混合物からなる群から選択される請求項１１に記載のデリバリーシステム。

１３．上記合成ポリマーが、ポリアクリレート、ポリメタクリレート、ポリビニルアセテート、ポリビニルアセテートフタレート、ポリ無水物、ポリ（２－ヒドロキシエチルメタクリレート）、ポリビニルアルコール、ポリジメチルシロキサン、シリコンエラストマー、それらの酸および塩基付加塩、およびそれらの混合物からなる群から選択される請求項１１に記載のデリバリーシステム。

１４．上記マトリックスが賦形剤を含む請求項１に記載のデリバリーシステム。

１５．上記賦形剤がマトリックス中に、マトリックスの重量に対して約０．０１％ないし約７５％存在する請求項１に記載のデリバリーシステム。

１６．上記賦形剤が、甘味剤、着色剤、界面活性剤、風味料、香料、ｐＨ調整剤、増量剤およびそれらの混合物からなる群から選択される請求項１に記載のデリバリーシステム。

１７．ａ）鎮痛薬、抗炎症薬、抗ヒスタミン薬、鎮咳薬、去痰薬、うっ血除去薬、麻酔薬、抗生物質、気管支収縮薬、心臓血管薬、中枢神経系薬、無機塩、ビタミン、金属塩およびそれらの混合物からなる群から選択される有効物質の有効量；ならびに

ｂ）（ｉ）約１０％ないし９５％量の約５０℃ないし約２００℃の範囲内の融点を有するワックスコア材；および（ii）約１％ないし約５０％の疏水性ポリマー材からなる空間的に配向されたマトリックス；ならびに

１００％までの残量の追加の賦形剤よりなる、実質的に味のない医薬デリバリー

システム。

１８．ａ）約５０℃ないし約２００℃の温度でワックスコア材および疏水性ポリマー材を配合および溶融してマトリックスを形成し；

ｂ）マトリックスを配合して成分の均質な混合物を形成し；

ｃ）マトリックスに有効物質を加えるが、マトリックスの温度は有効物質の分解温度未満に保持され；

ｄ）マトリックス内で有効物質を均質に分散して滑らかな分散体を得て；

ｅ）上記塊を凝固し、そして実質的に味のない医薬デリバリーシステムの粒子を形成することからなる実質的に味のない医薬デリバリーシステムを製造する方法。

１９．上記有効物質が医薬品である請求項１８に記載の方法。

２０．上記有効物質が、鎮痛薬、抗炎症薬、抗ヒスタミン薬、鎮咳薬、去痰薬、うっ血除去薬、麻酔薬、抗生物質、気管支収縮薬、心臓血管薬、中枢神経系薬、無機塩、ビタミン、金属塩およびそれらの混合物からなる群から選択される、請求項１８に記載の方法。

２１．段階ａ）におけるマトリックスの温度が７０℃ないし約１６０℃で保たれる請求項１８に記載の方法。

２２．賦形剤を、有効物質をマトリックス中に配合した後に混合物に加える請求項１８に記載の方法。

２３．上記賦形剤が、甘味剤、着色剤、界面活性剤、風味料、香料、ｐＨ調整剤、増量材およびそれらの混合物からなる群から選択される請求項１８に記載の方法。

２４．上記塊を凝結することにより上記段階ｄ）の滑らかな分散体を凝固させる請求項１８に記載の方法。

２５．上記段階ｄ）の滑らかな分散体を速やかに冷却しおよび凝結することにより薬剤の粒子を形成させる請求項１８に記載の方法。

２６．上記粒子を薬剤の有効量を含む医薬製品に形成する請求項１８に記載の方法。

２７．ワックスコア材がマトリックスの重量に対して約１０％ないし約９５％の量で存在し、疏水ポリマー材がマトリックスの重量に対して約１％ないし約５０％の量で存在する請求項１８に記載の方法。

２８．賦形剤が最終生成物の総成分量に基づいて１００％までの量で存在する請求項２３に記載の方法。

２９．賦形剤がマトリックスの重量に対して約０．０１％ないし約７５％の量で存在する請求項２８に記載の方法。

【発明の詳細な説明】

味を隠された医薬材料

発明の背景

発明の分野

本発明は、味を隠された医薬材料及びその製造方法に関するものである。更に特別には、本発明は、好適な味の組成物を製造するために、空間的に配向された疎水性マトリックス材料を使用して、悪い味の医薬に付随する有害な苦い味を隠すことに関するものである。

従来技術の説明

経口薬製剤は、多くの形態例えば液体溶液、乳化液又は懸濁液、並びに固体形態例えばカプセル又は錠剤として患者に投与される。錠剤又はカプセル形態で投与された製剤は通常、全体が飲まれる傾向がある。それ故、有効成分のしばしば不快な味は、薬が口内に存在する短時間の間、味が認識されることを妨げるための手段として以外には、医薬を製造する際に考慮される必要はない。前記手段は、マトリックス製剤内での有効成分の形成を包含してよい；カプセル、又は、口内に存在することを意図された短時間の間崩壊し始めないであろうような単に硬く圧縮された錠剤の使用。幾つかの製剤においては、好適でない味の粒子は、水溶性及び／又は非水溶性被覆剤、フィルム形成性ポリマー、水膨潤剤及び酸可溶性

剤を用いて被覆される。前記方法のうちの幾つかは、下記の特許に記載されている。

ハイリグ（Heilig）らによるアメリカ合衆国特許第２９５４３２２号明細書には、経口投与を目的とした錠剤が記載されており、この場合、錠剤全体がセラックとポリビニルピロリドンとの混合物で被覆されている。錠剤は全体が飲み込まれ且つ被膜は胃内で崩壊して有効成分を放出するであろうということが意図されている。

タンジ（Tansey）らによるアメリカ合衆国特許第３１３３８６３号明細書には、錠剤形態に圧縮され得る薬の顆粒の形成方法が記載されており、この場合、顆

粒は該顆粒を通って分散された種々のポリマーを包含する。一つの態様は、ＰＶＰ及びメチルセルロースと混合されたアセトアミノフェノンを含む。

ドウム（Daum）らによるアメリカ合衆国特許第３４２０９３１号明細書には、砂糖とＰＶＰのようなビニルポリマーとの混合物で被覆された糖衣薬剤〔“ドラジーズ（drageers）”〕が記載されている。この被膜はセルロース誘導体を含んでいてもよい。前記文献にはとりわけセルロース誘導体、例えばメチルセルロース、エチルセルロース、カルボキシメチルセルロース、ヒドロキシエチルセルロース、及びヒドロキシプロピルセルロースが記載されている。

ヒル（Hill）らによるアメリカ合衆国特許第３４５８６２２号明細書には制御放出錠剤が記載されており、この

場合、有効薬剤は、ＰＶＰとカルボキシビニル（ポリアクリル酸）親水性ポリマーからなるコア内に含まれている。

ワイス（Weiss）らによるアメリカ合衆国特許第４２５２７８６号明細書には、ヒル（Hill）のものと同様の制御放出錠剤が記載されており、この場合、有効薬剤を含むコアは、疎水性ポリマーと親水性ポリマーとの組み合わせからなる比較的不溶性で水透過性で破裂性のフィルムで被覆されている。セルロースアセテートが疎水性ポリマーポリマーのうちの一つとして記載されている。ワイス（Weiss）ら及びヒル（Hill）の錠剤は、全体を飲み込むことが意図されている。

ユー（Yu）らによるアメリカ合衆国特許第４４１５５４７号明細書には、水溶性フィルム形成性物質と水不溶性フィルム形成性物質とを用いてカプセル化された薬ペレットから基本的になる持続性放出薬錠剤が記載されている。素材が混合され、次いで圧縮性錠剤混合物を用いて錠剤形態に圧縮される。

チェルクリ（Cherukuri）らによるアメリカ合衆国特許第５０５９４１６号明細書には、ハイドロコロイドからなる第一の親水性被膜と、脂肪，ワックス及びそれらの混合物からなる群から選択された第二の疎水性被膜とを用いて被覆された亜鉛コア物質からなる亜鉛化合物デリバリーシステム（delivery system）の製造方法が記載されている。このデリバリーシステムは、亜鉛化合物の苦

いフレーバー性を隠す。

シャルマ（Sharma）らによるアメリカ合衆国特許第４５９７９７０号明細書には、

（A）少なくとも一種の天然又は人工甘味料と；

（B）（ｉ）レシチン、及び

（ii）（a）約１ないし約１０の沃素価を有する脂肪酸、

（b）天然ワックス、

（c）合成ワックス、及び

（d）それらの混合物

からなる群から選択された約２５℃ないし約１００℃の範囲内に融点を有する食用材料、並びに

（iii）少なくとも一種のグリセリド、

から基本的になる疎水性マトリックス

とからなる、コア物質の制御された放出を行うことが可能なデリバリーシステムが記載されている。

従来技術と異なり、本発明は、有効成分を被覆するために使用され、且つ味を隠すことと、水溶性有効成分及び非水溶性有効成分の両方の生物学的利用性の制御とを達成するマトリックス系の発見を指向している。

発明の要約

本発明は、

（a）有効物質（an active material）と、

（b）（ｉ）多量の約５０℃及び約２００℃の範囲内に融点

を有するワックスコア材（a wax core material）、並びに

（ii）少量の疎水性ポリマー材（a hydrophobic polymer material）からなる空間的に配向された（spatially oriented）マトリックス

とからなる実質的に味のない医薬デリバリーシステムに関するものである。

別の態様は、鎮痛薬、抗炎症薬、抗ヒスタミン薬、鎮咳薬、去痰薬、うっ血除去薬、麻酔薬、抗生物質、気管支拡張薬、心臓血管薬、中枢神経系薬、ビタミン

、金属塩、及びワックスコア材料と疎水性ポリマー材料とからなるマトリックス内に投入されたこれらの混合物からなる群から選択された薬である有効成分の使用方法を含む。

本発明の別の態様は、多量のワックスコア物質と少量の疎水性ポリマー材とを約５０℃ないし約２００℃の温度で溶融し且つ配合してマトリックスを形成し；前記マトリックスを混ぜ合わせて成分の均質混合物を形成し；前記マトリックスに有効物質を添加し；この場合、前記マトリックスの温度は前記有効物質の分解温度以下に保持し；前記マトリックス内に前記有効物質を均一に分散させてよく混ざった懸濁物を得；次いで前記素材を固化させて実質的に味のない医薬デリバリーシステムの粒子を形成することからなる実質的に味のない医薬デリバリーシステムの製造方法を含む。

発明の詳細な説明

本発明は、溶融したブレンド材中の医薬又は他の有効物質の溶融分散液及び／又は溶液を注型又は散布凝縮することによる味覚マスクシステムの製造を包含する。この方法により、実質的に無味の医薬デリバリーシステムが形成され、それは：（a）有効物質：そして（b）空間的に配向されたマトリックスであって（ｉ）主要量の、約５０℃と約２００℃の範囲内の融点を持つワックスコア材；および（ii）少量の、疎水性ポリマー材からなるマトリックスからなる。

有効成分又は医薬は単一成分又は複数成分の組み合わせとして記述されてよい。高い水溶性の医薬は直ぐ放出するシステムを形成すると期待され、他方、低い水溶性の医薬は制御された又は遅延した放出システムを形成するであろう。しかし、高い水溶性の医薬を使用して制御又は遅延放出システムも形成されるであろう。

術語「医薬」は、限定することなしに、薬剤、ビタミン、ミネラル補給剤、及び病気又は疾病の処置、予防、診断、治療又は軽減で使用することを意図する他の化学的又は生理学的物質、又は身体の構造又は機能に影響する物質を包含する。

本発明の集合体に使用できる医薬の適当な範疇は、広範囲にわたりそして概し

て安定な医薬の組み合わせを表す。具体的かつ特定の例は下記のものを包含する：

（a）鎮咳剤、例えばデキストロメトルファン、臭化水素酸デキストロメトルファン、ノスカピン、クエン酸カルベタペンタン及び塩酸クロフェジアノール；

（b）抗ヒスタミン剤、例えばマレイン酸クロフェニラミン、酒石酸フェニンダミン、マレイン酸ピリラミン、コハク酸ドキシラミン及びクエン酸フェニルトロキサミン；

（c）うっ血除去薬、例えば塩酸フェニレフリン、塩酸フェニルプロパノールアミン、塩酸プソイドエフェドリン、エフェドリン；

（d）いろいろのアルカロイド、例えばリン酸コデイン、硫酸コデインとモルヒネ；

（e）ミネラル補給剤；例えば塩化カリウム、塩化亜鉛及び炭酸カルシウム、酸化マグネシウムと他のアルカリ金属塩とアルカリ土類金属塩；

（f）緩下剤、ビタミン及び制酸剤；

（g）イオン交換樹脂、例えばコレスチラミン；

（h）抗コレステロール剤と抗脂質剤；

（i）抗不整脈剤、例えばＮ－アセチルプロカインアミド；

（j）解熱剤と鎮痛剤、例えばアセタミノフェン、アスピリンとイブプロフェン；

（k）食欲抑制剤、例えば塩酸フェニルプロパノールアミン又はカフェイン；及び

（l）去痰薬、例えばグアイフェネシン。

他の利用できる薬剤は下記のものを包含する：

抗炎症性物質、冠動脈拡張薬、脳動脈拡張薬、末梢血管拡張薬、抗感染薬、向精神薬、抗繰剤、刺戟薬、緩下薬、

胃腸鎮静薬、下痢止剤、抗狭心症剤、血管拡張薬、抗不整脈剤、抗高血圧薬、血

管収縮薬と片頭痛治療薬、抗生物質、トランキライザー、抗精神病薬、抗腫瘍薬、抗凝固薬と抗血栓薬、催眠薬、鎮静薬、鎮吐薬、制吐薬、鎮痙薬、神経筋薬、高血糖剤と低血糖剤、乾燥甲状腺製剤と抗甲状腺薬、利尿薬、抗痙攣薬、子宮弛緩薬、抗肥満薬、同化促進剤、赤血球生成剤、喘息治療薬、せき止薬（鎮咳剤）、粘液溶解剤、抗尿酸薬（anti-uricemic drugs）、等々。

医薬と薬剤との混合物も使用され得る。

特に不快な味のする医薬は下記のものを包含する：その不快度が最も強いと言われているピリドンカルボン酸系抗細菌剤、例えば５－アミノ－１－シクロプロピル－６，８－ジフルオロ－７－（シス－３，５－ジメチル－１－ピペラジニル）－１，４－ジヒドロ－４－オキソキノリン－３－カルボン酸、エノキサシン（Enoxacin）、ピペミジン酸（pipemidic acid）、シプロフロキサシン（Cyprofloxacin）、オフロキサシン（Ofloxacin）、及び／又はペフロキサシン（Pefloxacin）；抗てんかん薬、例えばゾニサミド（Zonisamide）；マクロライド系抗生物質、例えばエリスロマイシン；β－ラクタム系抗生物質、例えばペニシリン類とセファロスポリン類；向精神薬、例えばクロルプロマジン；スルピリン（Sulpyrine）のような医薬類；及びシメチジンのような抗潰瘍薬。

本発明の調製物は、不快味覚のマスキングに優れた効

果を持つので、これらの医薬の間で適当なものは、ピリドンカルボン酸系抗細菌剤、特に、５－アミノ－１－シクロプロピル－６，８－ジフルオロ－７－（シス－３，５－ジメチル－１－ピペラジニル）－１，４－ジヒドロ－４－オキソキノリン－３－カルボン酸又はエノキサシン（Enoxacin）である。うっ血除去剤の例は塩酸プソイドエフェドリンでありそしてミネラルは亜鉛塩であろう。

それら医薬は、それが薬学的に有効である量で使用された。医薬の有効量は使用される医薬に依存するというものの、本発明のマトリックス中へ、約５％ないし約６５％の量の医薬を容易に混和したが、その範囲では苦味のマスキングを発揮した。約６５％以上の量は、無味の特徴を喪失することになるだろう。

上述したように、味覚をマスクしたシステムは、いろいろな方法、例えば溶融したブレンド材中の医薬又は他の有効物質の溶融分散液及び／又は溶液を注型又

は散布凝縮することによって形成される。この方法でもって、味覚マスクしたシステムは硬化しつつある融解物と体液分散性／溶解性の材料中に分散されて懸濁液を形成する。次いで、その懸濁液は賦形剤でもって更に製剤化され、最終の投与型に使用される最終の投与型又は材料を形成する。

有効物質の不快味覚をマスクするのに使用される空間的に方向付けされたマトリックスは、２種の別々の成分；主要量の約５０℃と約２００℃の範囲内の融点を持つ

ワックスコア材；および少量の疎水性ポリマー材からなるマトリックスを含有しなければならない。

ワックスコア材は、マトリックスの約１０重量％ないし約９５重量％そして好ましくは約１５重量％ないし約８５重量％の量でマトリックス中に存在する。ワックスコア材は、常に疎水性ポリマーより多い量で存在しかくして主要量で存在していると記述されている。ここでは術語「コア」は、マトリックスの支柱成分を形成する物質を定義するのに使用される。

ワックスコア材は、広範囲の材料から選択される。特に好ましい材料は、１２ないし３２の炭素原子を持つ直鎖又は分枝鎖の、直鎖脂肪族の炭化水素、エステル、酸とアルコールからなる群から選択される。

特に好ましい材料は、動物蝋、植物蝋、石油ワックス、合成ワックス及びそれらの混合物、そして限定なしに、蜂蜜蝋、ラノリン、ステアリン酸、キャンデリア蝋、カルナウバ蝋、微結晶蝋、カルボワックス及びそれらの混合物から選択される。

疎水性ポリマー材は、マトリックスの約１重量％ないし５０重量％そして好ましくは約３重量％ないし約１０重量％の量でマトリックス中に存在する。上述したように、疎水性ポリマーはワックスコア材より少ない量で存在する。疎水性ポリマー材は、好ましくはワックスコア材中に若干の溶解性を持ちそしていろいろの天然ポリマー又はそれらの誘導体並びに合成ポリマーから選択され

る。天然ポリマーの例は下記のものを包含する：セルロース、酢酸セルロース、

フタル酸セルロース、メチルセルロース、エチルセルロース、ゼイン、医薬用グレーズ、シェラックワニス、ペクチン、ポリペプチド、それらの酸付加塩と塩基付加塩及びそれらの混合物。合成ポリマーの例は下記のものを包含する：ポリアクリレート類、ポリメタクリレート類、ポリ酢酸ビニル、アセテート　フタレート、ポリ酸無水物、ポリ（２－ヒドロキシエチルメタクリレート）、ポリビニルアルコール類、ポリジメチルシロキサン、シリコーンエラストマー、それらの酸付加塩と塩基付加塩、及びそれらの混合物。

ここで使用される術語「疎水性ポリマー」は、典型的には水に拮抗するポリマー材、換言すれば、ある程度の親水性の性質を持つ局部領域を分子中にたとへ持っていたとしても水に溶解することのできないポリマー材を指すものである。

ワックスコア材および疎水性ポリマー材の他に、マトリックスは、本明細書において賦形剤または添加剤と記載される追加の成分を含有し得る。例示される賦形剤は甘味料、着色剤、界面活性剤、フレーバー、芳香剤、ｐＨ調整剤、増量剤およびそれらの混合物を包含するが、これに限定されず、これらの成分はマトリックスの約０．０１ないし約７５重量％の量で使用され得る。

マトリックスを製造する際に、使用される材料の物性を考慮することが重要である。弾性またはプラスチック

特性を示す上記化合物は、カルナバのような非常に硬いワックスと異なり、マトリックスに対して最も適しているように見える。硬い天然ワックスから全体が構成されるマトリックスは望ましい作用を与えないけれども、硬い天然ワックスはマトリックスの一部に使用され得る。マトリックスの一部は脆い性質の共通トリグリセリド脂肪および／またはワックス、例えばカルナバを含有して、最終マトリックスの物性を変更することができる。この変更は生成物の凝固相での処理基準、またはその他の処理、例えば錠剤化もしくは乾燥粉末包装を満足させるために必要であるかもしれない。

ワックス溶融体配合物における適当なポリマーの溶解は得られる空間配向連続体（ＳＯＣ）のギップスの自由エネルギーを変更すると考えられている。疎水性ポリマーの存在は活性表面中心上での選択的吸着により溶融ワックス中に浸漬さ

れた有効物質の疎水化を補助する。

固体基材上のＳＯＣの拡張は包含される物質の化学ポテンシャルの変化の関数である「拡張係数」により記載される。特に、低融点固体、例えば有機ポリマー、ワックス、および共有結合化合物は一般的に１００ないし２５エルグ／ｃｍ²に及ぶ表面自由エネルギーを有する。固体基材の場合、表面および界面張力は基材上の湿潤液の接触角により個々に測定される。自然発生的なぬれに対し、この角度はゼロであるべきである。浸漬によるぬれを包含するシステム（系）に対し、接触角の要求はよ

り厳密性が低く、そして接触角が自然発生的である浸漬によるぬれのために９０度未満であることが要求されるのみである。

いくつかの変数は分散相の開放特性に影響を及ぼし得、そして粒径、粒径分散度および有効物質濃度の分散度、冷却または固化速度、およびシステム（系）の最終形態、例えば注型シートまたは凝固粒子を包含し得る。

有効成分（active components）の放出機構はいくつかの現象の組合せであるかもしれないと考えられている。マトリックスの酵素による分解、ＳＯＣを介する薬剤の拡散、競合的吸着、親水性表面中心から疎水性成分の放散、メソポアおよびマクロポアを介する薬剤の運搬、溶解によるマトリックス中への外部媒体の拡散または親水性ポリマーもしくは水溶性固体の添加により生成された多孔性構造を介する毛細管作用、薬剤粒子の不完全な被覆に起因するカプセル表面からの拡散、例えば被覆薬剤とマトリックスとの間の熱膨張の差により生じた亀裂、ＳＯＣの崩壊または浸食。

無味医薬デリバリーシステム（伝達系）は特定の有効成分のためのマトリックス成分および材料の最終用途を最初に選択することにより準備される。ワックス成分が溶解され、そして選択された疎水性ポリマー材はその溶融体に溶解される。このシステムにおける疎水性ポリマー材の組成は選択されたワックスに対して約１％ないし約５０％に及び、好ましいレベルはマトリックスの約３

重量％ないし約１０重量％である。温度は溶解を促進するために調整され、５０

℃ないし２００℃に及び、好ましくは７０℃ないし１６０℃である。疎水性ポリマー材が十分に配合されたら、追加のワックス成分が添加され、そして処理されて、均一ブレンドを得ることができる。追加のワックス成分の組成は最終マトリックスの全体量に対し０％ないし９９％を広範囲に変化し得るが、好ましくはマトリックスの４重量％ないし７５重量％である。有効成分が次に添加されて、最終混合物が形成されるが、追加のマトリックス成分に先立って有効成分を添加することによっても得ることができる。有効成分の分解を防止するために溶融体の温度を調整することがこの時点で必要であるかもしれない。

有効成分のスラリー化は簡単な撹拌により最初に行われ得る。しかしながら、ほとんどの場合において、凝集物のない滑らかな懸濁液を得るためには、高速ミキサーそして時にはコロイドミルを使用することが必要である。滑らかな懸濁液が得られたら、加工のための適当なレオロジー特性を与えるために温度を、好ましくは約７０℃ないし約１１０℃に再調整することが必要であるかもしれない。スラリーはもし必要ならば、当業者にはよく知られている方法を用いて凝固されるか、または急速に冷却され、そして粉砕される。得られる生成物の最終的な活性は１％ないし６０％、好ましくは１０％ないし５０％に及び得る。これらの最終的なシステムおよび材料

の組合せは有毒な薬剤物質を味覚マスキングするという予期せぬ効果を有する生成物を生じる。

特に好ましい方法において、実質的に無味の医薬デリバリーシステムの製造方法は、ａ）ワックスコア材および疎水性ポリマー材を約５０℃ないし約２００℃の温度で融解してマトリックスを形成し、ｂ）マトリックスをブレンドして各成分の均一な混合物を形成し、ｃ）有効物質をマトリックスに添加するが、ここでマトリックスの温度は有効物質の分解温度未満に維持される、ｄ）有効物質をマトリックス内に均一に分散して滑らかな懸濁液を得、ｅ）溶融材料をスプレーまたはスピン凝固させながら、素材を固化させて実質的に無味の医薬デリバリーシステムの粒子を形成する、ことからなる。得られる粒子は通常その粒径が約１０μと約４００μの間である。より大きい粒子は必要ならばさらなる加工のために

粉砕されてもよい。

味覚マスキングは本発明の重要な特徴であるので、舌下または頬への適用系における本発明の使用は意図されるが、一般的には好ましくはない。しかしながら、生成物が十分な時間、口腔内に滞留することが通常期待されないその他のシステムが意図される。従って、咀嚼可能および／または溶解可能な投与形態は本方法により特に改良されるであろう。さらに、液体経口投与形態はまた、本方法で特に改良されるであろう。

意図される一つの投与形態は、本発明の凝集体を含有するカプセルおよび／または本発明のデリバリーシステムを１種またはそれ以上の慣用の賦形剤と組み合わせて含有する物質中にゼラチンまたはその他のプラスチックマトリックスの使用を包含する。

本明細書において使用されている「賦形剤」という用語は凝集体の有効成分の特徴および機能を変えない医薬業界または食品業界において一般的に使用される物質および材料を意味する。

場合に応じてデリバリーシステムに添加され得るフレーバーは菓子製造業界において十分公知のものである。例えば、合成フレーバーオイル、および／または植物、葉、花、果実等からの油、およびそれらの組合せが有用である。

代表的なフレーバーオイルはスペアミント油、ハッカ油（ペパーミント油）、肉桂油（シナモン油）、冬緑油（サリチル酸メチル）を包含する。人工、天然または合成果実フレーバー、例えばレモン、オレンジ、ブドウ、ライムおよびグレープフルーツ等の柑橘類の油、およびリンゴ、イチゴ、サクランボ、パインアップル等の果実エッセンスもまた有用である。

使用される風味剤（フレーバー）の量は通常、フレーバーの種類、ベースの種類および望まれる強さ等の因子に対する好みの問題である。一般に、最終生成物の約０．５重量％ないし約５．０重量％の量が有用であり、約０．３重量％ないし約１．５重量％が好ましく、そし

て約０．８重量％ないし約１．２重量％が最も好ましい。

マトリックスは甘味剤を含有し得る。甘味剤は、水溶性甘味剤、水溶性合成甘味料、およびジペプチドをベースとした甘味料およびそれらの混合物を含むような材料の幅広い範囲内より選択され得る。特定の甘味料に限定されるわけではないが、代表例には以下のものが含まれる：

Ａ．水溶性甘味料、例えばモノサッカライド、ジサッカライドおよびポリサッカライド、例えばキシロース、リボース、グルコース、マンノース、ガラクトース、フラクトース、デキストロース、シュクロース、砂糖、マルトース、特に加水分解したスターチ、もしくはコーンシロップ固体および糖アルコール、例えばソルビトール、キシリトール、マンニトールおよびそれらの混合物。

Ｂ．水溶性合成甘味料、例えば溶性サッカリン塩、即ち、ナトリウムサッカリン塩もしくはカルシウムサッカリン塩、シクラミン酸塩、アセスルファムーＫ（acesulfam-K）等、および遊離酸形態のサッカリン。

Ｃ．ジペプチドをベースとした甘味料、例えばＬーアスパルチルＬーフェニルアラニンメチルエステルおよび米国特許発明明細書第３４９２１３１号において記載されているような材料等。

本発明に基づくデリバリーシステムは一般に固体もしくは半固体であるが、慣用の補助剤を用いてもしくは用いずに、システムの基本成分を、飲用しうる形態で摂取するために水もしくは他の摂取液体中に溶解もしくは分

散し得ようにして使用することが考えられる。

賦形剤はマトリックス中に加工中のいつでも添加される。異なる有効成分を均一にするために、ある種の賦形剤は、有効成分がマトリックスに混合される前、最中もしくは後に添加されると理解されるべきである。粉末の賦形剤は有効成分が添加される前もしくは後に添加されるのに対して、液体形態の賦形剤は、有効成分が添加される前に好ましくは添加される。

以下の実施例は本発明の好ましい態様を示すものであり、本発明を限定するためのものではない。全ての百分率は特に記載のない限り、マトリックスの重量当たりの百分率に基づくものでありそして全ての合計は１００重量％に等しい。

実施例１

この実施例は味のない塩酸プソイドエフェドリンの粒剤の製造を説明するものである。

７０ないし８０℃の温度において溶融しかつ均質の混合物を形成するために混合された密蝋（８１．６重量%）およびエチルセルロース（１０ｃｐｓ、３重量%）の懸濁液に、塩酸プソイドエフェドリン（１５．４重量%）を添加した。懸濁液を１０ないし１５分間混合し、そしてスピン凝結（spin congeallng）しながら空気中で冷却して固体粒子材料を製造した。スピン凝結された材料の粒子を、少なくとも５人よりなるパネル調査員が噛んだ場合に、製造物は苦い味がしなかった。

実施例２

この実施例はいくつかの形態の有効成分の製造を説明するものである。

溶融、混合および１２０℃の温度において維持された蜜蝋およびカルナウバ蝋もしくは商標名Witepsol（Huls America Inc. の脂肪トリグリセライド）（各８２重量%）およびエチルセルロース（１０ｃｐｓ、３重量%）の溶融ブレンドに、塩酸プソイドエフェドリン（１５重量%）を添加した。

カルナウバ蝋および商標名Witepsolをベースとして製造されたスラブを噛んだ場合に苦い味がしたが、一方で蜜蝋をベースとした粒剤およびスラブを噛んだ場合には苦い味はしなかった。従って、凝結の機構およびシステムのジオメトリーは味の差に影響をもたらす。

比較例Ａ

この実施例は比較のための蜜蝋のみによる粒剤の製造を説明するものである。

溶融した蜜蝋（８５重量%）を塩酸プソイドエフェドリンと混合することにより、実施例１の操作を繰り返した。

粒剤を噛んだ場合に苦い味がした。従って、疎水性ポリマー材の存在が、味を隠したシステムを作るのに要求される。

実施例３

この実施例は疎水性ポリマー材によるデリバリーシス

テムの製造を説明する。

蜜蝋（８２重量％）とエチルセルロース（１０ｃｐｓ　３重量％）もしくはメチルアクリレートポリマー（Rohm Pharmaより提供される商標名Eudragit RS100）（３重量％）のブレンドを使用して、実施例１の操作を繰り返した。材料をブロックの型にとりそして味を試験した。試験した場合に、どちらのシステムも苦い味がしなかった。従って、コアワックス材料中における疎水性ポリマー材の特性、例えば疎水性および混和性は、マトリックスの味を隠す特性に影響をもたらすことが結論づけられた。

実施例４

実施例１の操作を繰り返して、蜜蝋（それぞれ８９重量％および７２重量％）において、エチルセルロース、エトセル（Ethocel）（１０ｃｐｓ．，３重量％）のブレンド中に懸濁された６－メトキシエリスロマイシンＡ（それぞれ８重量％、１６重量％および２５重量％）からの粒剤を製造した。粒剤を噛んだ場合に、苦い味がしなかった。従って、これらのシステムは代換ドラッグ形態として適している。

実施例５

実施例１の操作を繰り返して、エチルセルロース、エトセル（１０ｃｐｓ．，３．００重量％）、蜜蝋（１７．００重量％）、ソルビタンモノロエート（sorbitan monoloeate）（３．００重量％）およびモノグリセライドおよびジグリセライド３６．９９重量％のブレンド中に懸濁したアセトアミノフェン（３５．３８重量％）、塩酸プソイドエフェドリン（３．３２重量％）、クロロフェニルアミンマレエート（０．２１重量％）およびデキストロメトファン（１．１０重量％）から粒剤を製造した。粒剤を噛んだ場合に、苦い味がしなかった。従って、これらのシステムはワックス混合物に適している。

実施例６

実施例１の操作を繰り返して、エチルセルロース（１０ｃｐｓ．，４．００重量％）、ソルビタンモノロエート（４．００重量％）、水素添加された植物油（８．００重量％）およびメキシコ周辺産のトウダイグサ科の低木のワックス（ca

ndelilla wax）（６４．００重量%）のブレンド中に懸濁されたアスコルビン酸（１９．８４重量%）および葉酸（０．１６重量%）からの粒剤を製造した。粒子粒剤を噛んだ場合に、酸っぱい味がしなかった。従って、これらのシステムはワックス混合物および他のワックス混合物に適している。

実施例７

実施例１の操作を繰り返して、エチルセルロース（１０ｃｐｓ．，３．００重量%）、ソルビタンモノロエート（３．００重量%）、蜜蝋（１２．２５重量%）、カルナウバ蝋（６．００重量%）およびモノグリセライドおよびジグリセライド（３５．７５重量%）のブレンド

中に懸濁されたイブプロフェン（４０．００重量%）からの粒剤を製造した。粒剤を噛んだ場合に、苦い味がしなかった。従って、これらのシステムはワックス混合物に適している。

本発明は記載されたとおりであり、多くの方法により同一の発明が多様化され得るものであることは明らかである。該変法は本発明の意図および範囲より逸脱するものとは認めらず、また全ての変法は以下の請求の範囲中に含まれるものである。

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11517

A. **CLASSIFICATION OF SUBJECT MATTER**
IPC(5) :A61K 9/14
US CL :424/484, 494; 426/5.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/484, 494; 426/5.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,790,991 (SHAW ET AL) 13 DECEMBER 1988; See entire document.	1-29
Y	US, A, 4,894,233 (SHARMA ET AL) 16 JANUARY 1990; See entire document.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be part of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 JANUARY 1994	21 MAR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. N/A	Authorized officer THURMAN K. PAGE Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

フロントページの続き

(72)発明者　リレイ，ジュニア．，トーマス　チャールズ
アメリカ合衆国，モンタナ州　63021　マンチェスター，ギャルウェイ　ドライヴ　762
(72)発明者　ラゴヴィヤー，ユーリィ
アメリカ合衆国，モンタナ州　63132　セントルイス，ブルックシア　レーン　8619　エィピーティー．エィ
(72)発明者　レヴィンソン，アール．ソウル
アメリカ合衆国，モンタナ州　63005　チェスターフィールド，キムウッド　コート　17020

Corresponding International Application of (2)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/14 — A1

(11) International Publication Number: WO 94/12157

(43) International Publication Date: 9 June 1994 (09.06.94)

(21) International Application Number: PCT/US93/11517

(22) International Filing Date: 26 November 1993 (26.11.93)

(30) Priority Data:
07/982,971 30 November 1992 (30.11.92) US

(71) Applicant: KV PHARMACEUTICAL COMPANY [US/US]; 2503 South Hanley Road, St. Louis, MO 63144-2555 (US).

(72) Inventors: CUCA, Robert, C.; 311 Edwards Drive, Edwardsville, IL 62025 (US). HARLAND, Roland, Scott; 1944 Schoettler Valley Drive, Chesterfield, MO 62017 (US). RILEY, Thomas, Charles, Jr.; 762 Galway Drive, Manchester, MO 63021 (US). LAGOVIYER, Yury; 8619 Brookshire Lane, Apartment A, St. Louis, MO 63132 (US). LEVINSON, R., Saul; 17020 Kimwood Court, Chesterfield, MO 63005 (US).

(74) Agent: NATH, Gary, M.; Nath, Amberly & Associates, 1835 K Street, N.W., Suite 750, Washington, DC 20006-1203 (US).

(81) Designated States: AU, CA, JP, KR, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: TASTEMASKED PHARMACEUTICAL MATERIALS

(57) Abstract

A substantially tasteless pharmaceutical delivery system, which comprises a) an active material; and b) a spatially oriented matrix comprising (i) a wax core material having a melting point within the range of about 50 °C and about 200 °C; and (ii) a regional hydrophobic polymer material and method for making the same.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

TASTEMASKED PHARMACEUTICAL MATERIALS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to tastemasked pharmaceutical materials and to methods for making the same. More particularly, the invention relates to tastemasking the noxious, bitter tastes associated with bad tasting drugs using a spatially oriented hydrophobic matrix material to prepare pleasant tasting compositions.

Description of the Prior Art

Oral pharmaceutical formulations are administered to patients in many forms, such as liquid solutions, emulsions, or suspensions, as well as in solid form such as capsules or tablets. Preparations administered in tablet or capsule form are usually intended to be swallowed whole. Therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except as a means to prevent the taste from being apparent during the short time that the medicine is in the mouth. Such means may include forming the active into a matrix preparation; the use of capsules or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth. In some preparations, the unpleasant tasting particles are coated with water-soluble and/or water-

insoluble coating agents, film forming polymers, water-swelling agents and acid soluble agents. Some of these procedures are described in the following patents.

U.S. Patent No. 2,954,322 to Heilig et al, discloses a tablet intended for oral administration wherein the whole tablet is coated with a mixture of shellac and polyvinylpyrrolidone. It is intended that the tablet be swallowed whole and that the coating will disintegrate in the stomach to release the active medicament.

U.S. Patent No. 3,133,863 to Tansey et al, discloses a method for forming granules of medicament that can be compressed into tablet form, wherein the granules include various polymers dispersed throughout the granules. One embodiment comprises acetaminophen mixed with PVP and methyl cellulose.

U.S. Patent 3,420,931 to Daum et al, discloses sugar-coated pharmaceutical preparations ("dragees") coated with a mixture of sugar and a vinyl polymer such as PVP. The coating may also contain cellulose derivatives. The reference specifically discloses cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.

U.S. Patent 3,458,622 to Hill discloses a controlled release tablet wherein the active medicament is contained in a core comprising a matrix of a mixture of PVP and a carboxyvinyl(polyacrylic acid)hydrophilic polymer.

U.S. Patent 4,252,786 to Weiss et al, discloses a controlled release tablet similar to that of Hill, wherein the core containing the active medicament is coated with a relatively insoluble, water permeable, rupturable film comprising a combination of hydrophobic and hydrophilic polymers. Cellulose acetate is disclosed as one of the hydrophobic polymers. The tablets of Weiss et al. and Hill are intended to be swallowed whole.

U.S. Patent No. 4,415,547 to Yu et al, discloses sustained release pharmaceutical tablets consisting essentially of drug pellets encapsulated with a water-soluble film-forming substance and a water-insoluble film-forming substance. The materials are blended and compressed into tablet form with a compressible tableting mixture.

U.S. Patent 5,059,416 to Cherukuri et al, discloses a process for preparing a zinc compound delivery system comprised of a zinc core material coated with a first hydrophilic coating comprising a hydrocolloid material and a second hydrophobic coating selected from the group consisting of fats, waxes and mixtures thereof. The delivery system masks the bitter flavor characteristic of zinc compounds.

U.S. Patent 4,597,970 to Sharma et al, discloses a delivery system capable of effecting a controlled release of core material comprising: (A) at least one natural or artificial sweet material; and (B) a hydrophobic matrix consisting essentially of (i) lecithin; and (ii) an edible material having a melting point in the range of about 25°C

to about 100°C selected from the group consisting of (a) fatty acids having an iodine value of about 1 to about 10, (b) natural waxes, (c) synthetic waxes and (d) mixtures thereof; and (iii) at least one glyceride.

Unlike the prior art, the present invention is directed to the discovery of a matrix system that can be used to coat the active component and which achieves a good balance between tastemasking and control of bioavailability of both water-soluble and insoluble active components.

SUMMARY OF THE INVENTION

This invention relates to a substantially tasteless pharmaceutical delivery system, comprising: (a) an active material and (b) a spatially oriented matrix comprising (i) a major amount of a wax core material having a melting point within the range of about 50°C and about 200°C; and (ii) a minor amount of a hydrophobic polymer material.

An alternative embodiment involves use of an active material which is a drug selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof disbursed within a matrix comprising a wax core material and a hydrophobic polymer material.

A further embodiment of the invention involves a process for preparing a substantially tasteless pharmaceutical delivery system, comprising melting and

blending a major amount of a wax core material and a minor amount of a hydrophobic polymer material at a temperature from about 50°C to about 200°C to form a matrix; blending the matrix to form a homogenous mixture of components; adding the active material to the matrix, wherein the temperature of the matrix is maintained below the decomposition temperature of the active material; uniformly dispersing the active material within the matrix to obtain of smooth suspension; and solidifying the mass to form particles of the substantially tasteless pharmaceutical delivery system.

DETAILED DESCRIPTION OF THE INVENTION

The present invention involves the preparation of a tastemasked system by casting or spin congealing melt dispersions and/or solutions of drug or other active material in a molten blend of materials. In this manner a substantially tasteless pharmaceutical delivery system is formed which comprises: (a) an active material; and (b) a spatially oriented matrix comprising (i) a major amount of wax core material having a melting point within the range of about 50°C and about 200°C; and (ii) a minor amount of a hydrophobic polymer material.

The active(s) or drug(s) may be described as a single drug entity or a combination of entities. A drug with high water-solubility is expected to produce immediate release systems, whereas a drug with low water-solubility may produce a controlled or delayed release system. However,

controlled or delayed release systems may result when using drugs with high water-solubility. The term "drug" includes without limitations, medicaments, vitamins, mineral supplements and other chemical or biological substances intended for use in the treatment, prevention, diagnosis, cure or mitigation of disease or illness, or substances which affect the structure or function of the body.

Suitable categories of drugs that may be employed in the instant aggregate may vary widely and generally represent any stable drug combination. Illustrative categories and specific examples include: (a) antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride; (b) antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate; (c) decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine; (d) various alkaloids, such as codeine phosphate, codeine sulfate and morphine; (e) mineral supplements such as potassium chloride, zinc chloride and calcium carbonates, magnesium oxide and other alkali metal and alkaline earth metal salts; (f) laxatives, vitamins and antacids; (g) ion exchange resins such as cholestyramine; (h) anti-cholesterolemic and anti-lipid agents; (i) antiarrhythmics such as N-acetylprocainamide; (j) antipyretics and analgesics such as acetaminophen, aspirin

and ibuprofen; (k) appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and (l) expectorants such as guaifenesin.

Additional useful active medicaments include anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodialators, anti-infectives, psychotropics, antimanics, stimulants, laxatives, gastro-intestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-arrythmics, antihypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, antipsychotics, antitumor drugs, anticoagulants and antithrombotic drugs, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants (anti-tussives), mucolytics, anti-uricemic drugs, and the like.

Mixtures of the drugs and medicaments may also be used.

Particular unpleasant tasting drugs include pyridonecarboxylic acid antibacterial agents whose degree of unpleasantness is said to be strongest, such as 5-amino-1-cyclopropyl-6,8-difluoro-7-(cis-3,5-dimethyl-1-piperazinyl)-1,4-dihydro-4-(oxoquinoline-3-carboxylic acid, Enoxacin, Pipemidic acid, Ciprofloxacin, Ofloxacin, and Pefloxacin; antiepileptic drugs such as Zonisamide; macrolide antibiotics such as Erythromycin; beta-lactam antibiotics

such as penicillins or cephalosporins; psychotropic drugs such as Chlorpromazine; drugs such as Sulpyrine; and antiulcer drugs such as Cimetidine. Suitable among these drugs are pyridonecarboxylic acid antibacterial agents, especially 5-amino-1-cyclopropyl-6,8-difluoro-7-(cis-3,5-dimethyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid or Enoxacin, because the preparations of this invention have an excellent effect of masking the unpleasant taste. An exemplary decongestant is pseudoephedrine hydrochloride and mineral would be zinc salts.

The drugs were used in amounts that are therapeutically effective. While the effective amount of a drug will depend on the drug used, amounts of drug from about 5% to about 65% have been easily incorporated into the present matrix while achieving bitter taste masking. Amounts above about 65% may result in the loss of tasteless properties.

As indicated above, the tastemasked systems may be formed in a variety of ways, such as casting or spray congealing melt dispersions and/or solutions of active in a molten blend of materials. In this way, the tastemasked systems are dispersed in melt hardening and body fluid dispersable/dissolvable materials to form a suspension. The suspensions may then be further formulated with excipient materials to form the final dosage form or material to be used in the final dosage form.

The spatially oriented matrix used to mask the unpleasant taste of the active material must contain two separate components; a major amount of a wax core material having a melting point within the range of about 50°C to about 200°C and a separate minor amount of a hydrophobic polymer material.

The wax core material is present in the matrix in amounts of about 10% to about 95% and preferably about 15% to about 85% by weight of the matrix The wax core material is always present in amounts greater than the hydrophobic polymer and thus has been described as being present in a major amount. The term "core" is used herein to define the substance forming the backbone component of the matrix.

The wax core material may be chosen from a wide variety of materials. Particularly preferred materials are selected from the group consisting of long chain fatty hydrocarbons, esters, acids and alcohols of straight or branched chain alkyls having from 12 to 32 carbon atoms.

Particularly preferred materials are selected from animal waxes, vegetable waxes, petroleum waxes, synthetic waxes, and mixtures thereof and include without limitation beeswax, lanolin, stearic acid, candelilla wax, carnauba wax, microcrystalline wax, carbowax and mixtures thereof.

The hydrophobic polymer material is present in the matrix in amounts of about 1% to about 50% and preferably about 3% to about 10% by weight of the matrix. As discussed above, the hydrophobic polymer is present in amounts less than the wax core material. The hydrophobic polymer

material is preferably a material that has some solubility in the wax core material and is selected from a variety of natural polymers or derivative thereof as well as synthetic polymers. Exemplary natural polymers include cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, ethyl cellulose, zein, pharmaceutical glaze, shellac, chitan, pectin, polypeptides, acid and base addition salts thereof, and mixtures thereof. Exemplary synthetic polymers include polyacrylates, polymethacrylates, polyvinyl acetate, acetate phthalate, polyanhydrides, poly(2-hydroxyethyl methacrylate), polyvinylalcohols, polydimethyl siloxone, silicone elastomers, acid and base addition salts thereof, and mixtures thereof. The term "hydrophobic polymer" as used herein refers to polymeric materials that are typically antagonistic to water, i.e., incapable of dissolving in water even though they may have regional areas in the molecule that have some hydrophilic properties.

In addition to the wax core material and the hydrophobic polymer material, the matrix may contain additional ingredients, herein referred to as excipients or additives. Exemplary excipients include, but are not limited to sweetening agents, colorants, surfactants, flavors, fragrances, pH modifiers, bulking agents, and mixtures thereof which components may be used in an amount of about .01% to about 75% by weight of the matrix.

When preparing the matrix, it is important to consider the physical properties of the materials used. Those compounds which exhibit an elasticity or plastic property

appear to be best suited for the matrix, as opposed to very hard waxes such as carnauba. Through a matrix composed completely of a hard natural wax does not give the desired effect, hard natural wax can be used in a portion of the matrix. Portions of the matrix may contain common triglyceride fats and or waxes of a brittle nature such as carnauba to modify physical characteristics of the final matrix. This modification may be necessary to satisfy processing criteria at the congealing phase of the product, or further processing such as tableting or dry powder packaging.

It is believed that dissolution of appropriate polymers in the wax melt formulations modifies the Gibbs Free Energy of the resulting spatially oriented continuum (SOC). The presence of the hydrophobic polymer aids the hydrophobization of the active material immersed in the melt wax by virtue of selective adsorption onto active surface centers.

Spreading of a SOC on a solid substrate is described by the "spreading coefficient" which is a function of the changes of the chemical potentials of the materials involved. Particularly, low-melting solids, such as organic polymers, waxes, and covalent compounds, in general have surface free energies ranging from 100 to 25 ergs/cm^2. In the case of a solid substrate, the surface and interfacial tensions are measured individually by contact angle of the wetting liquid on the substrate. For spontaneous wetting this angle should be zero. For the system which involves

immersional wetting, the contact angle requirement is less stringent and only requires the contact angle to be less than 90 degrees for immersional wetting to be spontaneous.

Several variables may effect the release characteristics of the dispersed phase and include, particle size, particle size distribution and distribution of the active, material concentration, cooling or solidification rates and conditions, and final form of the system, such as cast sheets or congealed particles.

It is believed that the release mechanism of active components may be a combination of several phenomena. Enzymatic degradation of the matrix, diffusion of the drug through the SOC, competitive adsorption, desorption of hydrophobic components from hydrophilic surface centers, convection of the drug through mesopores and macropores, diffusion of the external medium into the matrix by way of solubility or capillary action through porous structures created by the addition of hydrophilic polymers or water-soluble solids, diffusion from the surface of a capsule due to incomplete coating of drug particles, cracks caused for instance by the difference in thermal expansion between coated drug and matrix, disintegration or erosion of the SOC.

The tasteless pharmaceutical delivery system is prepared by first selecting the matrix components for the particular active ingredient and end use of material. The wax component is melted, and the selected hydrophobic polymer material dissolved in the melt. The composition of

hydrophobic polymer material in this system ranges from about 1% to about 50% relative to the selected wax, with preferred levels from about 3% to about 10% by weight of the matrix. Temperatures are adjusted to facilitate the solution, ranging from 50°C to 200°C, with preferred temperatures from 70°C to 160°C. Once the hydrophobic polymer material is incorporated satisfactorily, additional wax components can be added and processed to obtain a uniform blend. The composition of additional wax components may vary widely from 0% to 99% relative to the total content of the final matrix but are preferably from 4% to 75% by weight of the matrix. The active ingredients are then added to form the final mixture, which can also be obtained by adding the active ingredients prior to the additional matrix components. It may be necessary at this point to adjust the temperature of the melt to prevent decomposition of the active ingredient.

Slurring of the active ingredient can initially be done by simple stirring. However, in most cases it is necessary to use a high speed mixer and sometimes a colloid mill to obtain a smooth suspension, free of agglomerates. Once a smooth suspension is obtained, it may be necessary to readjust the temperature to provide the proper rheological characteristics for processing, preferably from about 70°C to about 110°C. The slurry is congealed using technology well known to the ordinary skilled artisan or rapidly cooled and ground, if required. The final activity of the resultant product may range from 1% to 60%, preferably from

10% to 50%. These final systems and combination of materials result in product with unanticipated benefits of tastemasking noxious drug substances.

In a particularly preferred procedure, a process for preparing a substantially tasteless pharmaceutical delivery system comprises: a) melting a wax core material and a hydrophobic polymer material at a temperature from about 50°C to about 200°C to form a matrix; b) blending the matrix to form a homogenous mixture of components; c) adding the active material to the matrix, wherein the temperature of the matrix is maintained below the decomposition temperature of the active material; d) uniformly dispersing the active material within the matrix to obtain of smooth suspension; e) solidifying the mass while spray or spin congealing the molten material to form particles of the substantially tasteless pharmaceutical delivery system. The particles obtained are usually between about 10μ to about 400μ in size. Larger particles may be ground if required for further processing.

Since tastemasking is a key feature of the invention, the use of the invention in sublingual or buccal systems is contemplated, but not generally preferred. However, other systems in which the product would not normally be expected to be retained in the mouth for significant amounts of time are contemplated. Thus, chewable and/or dissolvable dosage forms would be particularly improved with this technology. Further, fluid oral dosage forms would also be particularly improved with this technology.

One dosage form contemplated, involves the use of gelatin or other plastic matrix(es) in a capsule containing the inventive aggregate and/or materials containing the inventive delivery system in combination with one or more conventional excipients.

The term "excipients" as used herein mean substances and materials generally used in the drug or food industry which do not alter the character and function of the active component of the aggregate.

Flavors which may optionally be added to the delivery system are those well known in the confectionery art. For example, synthetic flavor oils, and/or oils from plants, leaves, flowers, fruits and so forth, and combinations thereof are useful.

Representative flavor oils include spearmint oil, peppermint oil, cinnamon oil, and oil of wintergreen (methylsalicylate). Also useful are artificial, natural or synthetic fruit flavors such as citrus oils including lemon, orange, grape, lime, and grapefruit, and fruit essences including apple, strawberry, cherry, pineapple and so forth.

The amount of flavoring agent employed is normally a matter of preference subject to such factors as flavor type, base type and strength desired. In general, amounts of about 0.05% to about 5.0% by weight of the final product are useful with amounts of about 0.3% to about 1.5% being preferred and about 0.8% to about 1.2% being most preferred.

The matrix may contain a sweetening agent. Sweetening agents may be selected from a wide range of materials such as water-soluble sweetening agents, water-soluble artificial sweeteners, and dipeptide based sweeteners, including mixtures thereof. Without being limited to particular sweeteners, representative illustrations encompass:

A. Water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof.

B. Water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, acesulfam-K and the like, and the free acid form of saccharin.

C. Dipeptide based sweeteners such as L-aspartyl L-phenylalanine methyl ester and materials described in U.S. Patent No. 3,492,131 and the like.

While delivery systems based on the instant invention are generally solid or semi-solid, it is contemplated that they may be employed, with or without the conventional supplemental agents, as principal components of systems to be dissolved or dispersed in water or other ingestible liquids for ingestion in a drinkable form.

The excipients are added to the matrix anytime during processing. It should be recognized that certain excipients should be added prior to, during or after the active material is blended into the matrix in order to achieve uniform distinction of the ingredients. Preferably, excipients in liquid form are added before the active material whereas powdered excipients may be added before or after the active material is added.

The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All percentages are based on the percent by weight of the matrix unless otherwise indicated and all totals equal 100% by weight.

EXAMPLE 1

This example demonstrates the production of tasteless granules of pseudoephedrine hydrochloride.

To a suspension of beeswax (81.6% w/w) and ethyl cellulose (10 cps, 3% w/w) which was melted at a temperature of 70-80°C and blended to form a homogenous mixture was added pseudoephedrine hydrochloride (15.4% w/w). The suspension was blended for 10-15 minutes, and cooled in air while spin congealing to form a solid particulate material. Particles of spin congealed material when chewed by a panel comprising at least five members, the product did not exhibit any bitter taste.

EXAMPLE 2

This example demonstrates the production of various forms of active material.

To a molten blend of beeswax, carnauba wax or Witepsol® (a triglyceride fat of Hüls America Inc.) each at (82% w/w) and ethyl cellulose (10 cps, 3% w/w) which were melted, blended and maintained at a temperature of 120°C was added pseudoephedrine hydrochloride (15% w/w).

The slabs produced that were based on carnauba wax and Witepsol® when chewed exhibited a bitter taste, while granules and slabs based on beeswax when chewed did not exhibit a bitter taste. Therefore, the mechanism of congealing and geometry of the system influence the degree of taste.

COMPARATIVE EXAMPLE A

This example demonstrates the production of comparative granules with beeswax alone.

The procedure of Example 1 was repeated with melted beeswax (85% w/w) blended with pseudoephedrine hydrochloride (15% w/w).

The granules when chewed exhibited a bitter taste. Therefore the presence of the hydrophobic polymer material is required to create a tastemasked system.

EXAMPLE 3

This example demonstrates the preparation of a delivery system with a hydrophobic polymer material.

The procedure of Example 1 was repeated using a blend of beeswax (82% w/w) with ethyl cellulose (10 cps 3% w/w) or a methylacrylate polymer (Eudragit® RS100 by Rohm Pharma) (3% w/w). The material was cast into a block and taste tested. Neither of the systems exhibited a bitter taste when tested. It is therefore concluded that the hydrophobic polymer material properties such as hydrophobicity and miscibility in the core wax material influence the tastemasking properties of the matrix.

EXAMPLE 4

The procedure of Example 1 was repeated to prepare granulars from 6-methoxy erythromycin A (8%, 16% and 25% w/w respectively) suspended in a blend of ethyl cellulose, Ethocel (10 cps., 3% w/w), in beeswax (89% and 72% w/w, respectively). The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to alternative drug forms.

EXAMPLE 5

The procedure of Example 1 was repeated to prepare granulars from acetaminophen (35.38% w/w), pseudoephedrine hydrochloride (3.32% w/w), chloropheniramine maleate (0.21% w/w) and dextromethorphan (1.10% w/w) suspended in a blend of ethyl cellulose, Ethocel (10 cps, 3.00% w/w), beeswax

(17.00% w/w), sorbitan monoloeate, 3.00% w/w and mono- and di-glycerides, 36.99% w/w. The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to wax mixtures.

EXAMPLE 6

The procedure of Example 1 was repeated to prepare granulars from ascorbic acid (19.84% w/w) and folic acid (0.16% w/w) suspended in a blend of ethyl cellulose, (10 cps., 4.00% w/w) sorbitan monoloeate (4.00% w/w), hydrogenated vegetable oil, (8.00% w/w) and candelilla wax (64.00% w/w). The particle granulars when chewed did not exhibit a sour taste. Therefore, these systems are applicable to wax mixtures and other wax materials.

EXAMPLE 7

The procedure of Example 1 was repeated to prepare granulars from ibuprofen (40.00% w/w) suspended in a blend of ethyl cellulose, (10 cps., 3.00% w/w), sorbitan monoleate (3.00% w/w), beeswax (12.25% w/w) carnauba wax (6.00% w/w) and mono- and di- glycerides (35.75% w/w). The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to wax mixtures.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A substantially tasteless pharmaceutical delivery system, which comprises:

a) an active material; and

b) a spatially oriented matrix comprising:

(i) a major 10-95% amount of a wax core material having a melting point within the range of about 50°C and about 200°C; and

(ii) a less than 50% minor amount of hydrophobic polymer material.

2. The delivery system of claim 1, wherein the active material is a pharmaceutical drug.

3. The delivery system of claim 1, wherein the active material is selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof.

4. The delivery system of claim 1, wherein the wax core material is present in an amount of about 10% to about 95% by weight of the matrix.

5. The delivery system of claim 1, wherein the wax core material is present in an amount of about 15% to about 85% by weight of the matrix.

6. The delivery system of claim 1, wherein the wax core material is selected from the group consisting of long chain fatty hydrocarbons, esters, acids and alcohols of straight or branched chain alkyls having from 12 to 32 carbon atoms.

7. The delivery system of claim 6, wherein the wax core material is selected from the group consisting of animal waxes, vegetable waxes, petroleum waxes, synthetic waxes, and mixtures thereof.

8. The delivery system of claim 7, wherein the wax core material is selected from the group consisting of beeswax, lanolin, stearic acid, candelilla wax, carnauba wax, microcrystalline wax, carbowax and mixtures thereof.

9. The delivery system of claim 1, wherein the hydrophobic polymer material is present in an amount of about 1% to about 50% by weight of the matrix.

10. The delivery system of claim 1, wherein the hydrophobic polymer material is present in an amount of about 3% to about 10% by weight of the matrix.

11. The delivery system of claim 1, wherein the hydrophobic polymer material is a natural polymer or synthetic polymer.

12. The delivery system of claim 11, wherein the natural polymer is selected from the group consisting of cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, ethyl cellulose, zein, pharmaceutical glaze, shellac, chitan, pectin, polypeptides, acid and base addition salts thereof, and mixtures thereof.

13. The delivery system of claim 11, wherein the synthetic polymer is selected from the group consisting of polyacrylates, polymethacrylates, polyvinyl acetate, polyvinyl acetate phthalate, polyanhydrides, poly(2-hydroxyethyl methacrylate), polyvinylalcohols, polydimethyl siloxone, silicone elastomers, acid and base addition salts thereof, and mixtures thereof.

14. The delivery system of claim 1, wherein the matrix includes an excipient.

15. The delivery system of claim 1, wherein the excipient is present in the matrix in an amount of about .01% to about 75% by weight of the matrix.

16. The delivery system of claim 1, wherein the excipient is selected from the group consisting of sweetening agents, colorants, surfactants, flavors, fragrances, pH modifiers, bulking agents, and mixtures thereof.

17. A substantially tasteless pharmaceutical delivery system which comprises:

a) an effective amount of an active material selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof; and

b) a spatially oriented matrix comprising:

(i) from about 10% to about 95% of a wax core material having a melting point within the range of about 50°C and about 200°C; and

(ii) from about 1% to about 50% of a hydrophobic polymer material; and remaining amount up to 100% of an additional excipient.

18. A process for preparing a substantially tasteless pharmaceutical delivery system, which comprises:

a) blending and melting a wax core material and a hydrophobic polymer material at a temperature from about 50°C to about 200°C to form a matrix;

b) blending the matrix to form a homogenous mixture of components;

c) adding the active material to the matrix, wherein the temperature of the matrix is maintained below the decomposition temperature of the active material;

d) uniformly dispersing the active material within the matrix to obtain of smooth dispersion;

e) solidifying the mass and forming particles of the substantially tasteless pharmaceutical delivery system.

19. The process of claim 18, wherein the active material is a pharmaceutical drug.

20. The process of claim 18, wherein the active material is selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics,

antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof.

21. The process of claim 18, wherein the temperature of the matrix in step a) is maintained at from 70°C to about 160°C.

22. The process of claim 18, wherein an excipient is added to the mixture after the active material is blended into the matrix.

23. The process of claim 22, wherein the excipient is selected from the group consisting of sweetening agents, colorants, surfactants, flavors, fragrances, pH modifiers, bulking agents, and mixtures thereof.

24. The process of claim 18, wherein the smooth dispersion of step d) is solidified by congealing the mass.

25. The process of claim 18, wherein the smooth dispersion of step d) is rapidly cooled and congealed to form particles of drug.

26. The process of claim 18, wherein the particles are formed into a pharmaceutical product containing an effective amount of drug.

27. The process of claim 18, wherein the wax core is present in amounts of about 10% to about 95% by weight of the matrix, the hydrophobic polymer material is present in amounts of about 1% to about 50% by weight of the matrix.

28. The process of claim 23, wherein the excipient is present in amounts up to 100% based on the weight of total components in the final product.

29. The process of claim 28, wherein the excipient is present in amounts from about .01% to about 75% by weight of the matrix.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11517

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/14
US CL :424/484, 494; 426/5, 2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484, 494; 426/5, 2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,790,991 (SHAW ET AL) 13 DECEMBER 1988; See entire document.	1-29
Y	US, A, 4,894,233 (SHARMA ET AL) 16 JANUARY 1990; See entire document.	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
27 JANUARY 1994	21 MAR 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. N/A	Authorized officer THURMAN K. PAGE Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

Corresponding US Application of (2)

US005494681A

United States Patent [19]

Cuca et al.

[11] Patent Number: 5,494,681

[45] Date of Patent: Feb. 27, 1996

[54] **TASTEMASKED PHARMACEUTICAL MATERIALS**

[75] Inventors: **Robert C. Cuca**, Edwardsville, Ill.; **Ronald S. Harland**, Chesterfield, Mo.; **Thomas C. Riley, Jr.**, Manchester, Mo.; **Yury Lagoviyer**, St. Louis, Mo.; **R. Saul Levinson**, Chesterfield, Mo.

[73] Assignee: **KV Pharmaceutical Company**, St. Louis, Mo.

[21] Appl. No.: **288,849**

[22] Filed: **Aug. 11, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 982,971, Nov. 30, 1992, abandoned.

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/484**; 424/489; 424/495; 424/494; 424/502

[58] **Field of Search** 424/484, 489, 424/490, 491

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,954,322	9/1960	Heilig et al.	424/481
3,133,863	5/1964	Tansey	424/465
3,420,931	1/1969	Daum et al.	424/479
3,458,622	7/1969	Hill	424/468
3,806,603	4/1974	Gaunt et al.	514/783
3,860,733	1/1975	Morse et al.	426/302
3,879,511	4/1975	Goodhart et al.	424/495
3,950,508	4/1976	Mony et al.	424/465
4,117,801	10/1978	Dannelly et al.	118/20
4,140,756	2/1979	Gallian	424/21
4,252,786	2/1981	Weiss et al.	424/495
4,415,547	11/1983	Yu et al.	424/469
4,590,075	5/1986	Wei et al.	426/5
4,597,970	7/1986	Sharma et al.	426/5
4,716,041	12/1987	Kjornaes et al.	424/468
4,747,881	5/1988	Shaw et al.	424/476
4,790,991	12/1988	Shaw et al.	424/441
4,800,087	1/1989	Mehta	424/497
4,806,603	2/1989	Hess et al.	525/445
4,810,501	3/1989	Ghebre-Sallassie	424/469
4,816,265	3/1989	Cherukuri et al.	426/5
4,818,539	4/1989	Shaw et al.	424/441
4,843,098	6/1989	Shaw et al.	424/476
4,851,226	7/1989	Julian et al.	424/441
4,851,392	7/1989	Shaw et al.	424/441
4,865,851	9/1989	James et al.	424/498
4,916,161	4/1990	Patell	514/570
4,925,674	5/1990	Giannini et al.	424/469
4,931,293	6/1990	Cherukuri et al.	426/5
4,933,190	6/1990	Cherukuri et al.	426/5
4,946,685	8/1990	Edgren et al.	424/472
4,966,770	10/1990	Giannini et al.	424/461
4,981,698	1/1991	Cherukuri et al.	348/415
5,004,595	4/1991	Cherukuri et al.	424/48
5,013,557	5/1991	Tai	424/493
5,026,560	6/1991	Makino et al.	424/494
5,057,319	10/1991	Gottwald et al.	424/441
5,059,416	10/1991	Cherukuri et al.	424/48
5,075,114	12/1991	Roche	424/470
5,082,669	1/1992	Shirai et al.	424/495
5,084,278	1/1992	Mehta	424/441
5,085,868	2/1992	Mattsson et al.	424/490
5,098,714	3/1992	Wright et al.	424/423

FOREIGN PATENT DOCUMENTS

WO92/12704	8/1992	European Pat. Off. .
1462193	12/1966	France .

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Nath & Associates; Gary M. Nath; Suet M. Chong

[57] **ABSTRACT**

A substantially tasteless pharmaceutical delivery system, which comprises a) an active material; and b) a spatially oriented matrix comprising (i) a wax core material having a melting point within the range of about 50° C. and about 200° C.; and (ii) a regional hydrophobic polymer material and method for making the same.

14 Claims, No Drawings

TASTEMASKED PHARMACEUTICAL MATERIALS

This application is a continuation application of U.S. patent application Ser. No. 07/982,971, filed Nov. 30, 1992, abandoned, the entire contents of which are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to tastemasked pharmaceutical materials and to methods for making the same. More particularly, the invention relates to tastemasking the noxious, bitter tastes associated with bad tasting drugs using a spatially oriented hydrophobic matrix material to prepare pleasant tasting compositions.

2. Description of the Prior Art

Oral pharmaceutical formulations are administered to patients in many forms, such as liquid solutions, emulsions, or suspensions, as well as in solid form such as capsules or tablets. Preparations administered in tablet or capsule form are usually intended to be swallowed whole. Therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except as a means to prevent the taste from being apparent during the short time that the medicine is in the mouth. Such means may include forming the active into a matrix preparation; the use of capsules or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth. In some preparations, the unpleasant tasting particles are coated with water-soluble and/or water-insoluble coating agents, film forming polymers, water-swelling agents and acid soluble agents. Some of these procedures are described in the following patents.

U.S. Pat. No. 2,954,322 to Heilig et al, discloses a tablet intended for oral administration wherein the whole tablet is coated with a mixture of shellac and polyvinylpyrrolidone. It is intended that the tablet be swallowed whole and that the coating will disintegrate in the stomach to release the active medicament.

U.S. Pat. No. 3,133,863 to Tansey et al, discloses a method for forming granules of medicament that can be compressed into tablet form, wherein the granules include various polymers dispersed throughout the granules. One embodiment comprises acetaminophen mixed with PVP and methyl cellulose.

U.S. Pat. No. 3,420,931 to Daum et al, discloses sugar-coated pharmaceutical preparations ("dragees") coated with a mixture of sugar and a vinyl polymer such as PVP. The coating may also contain cellulose derivatives. The reference specifically discloses cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.

U.S. Pat. No. 3,458,622 to Hill discloses a controlled release tablet wherein the active medicament is contained in a core comprising a matrix of a mixture of PVP and a carboxyvinyl(polyacrylic acid)hydrophilic polymer.

U.S. Pat. No. 4,252,786 to Weiss et al, discloses a controlled release tablet similar to that of Hill, wherein the core containing the active medicament is coated with a relatively insoluble, water permeable, rupturable film comprising a combination of hydrophobic and hydrophilic polymers. Cellulose acetate is disclosed as one of the hydrophobic polymers. The tablets of Weiss et al. and Hill are intended to be swallowed whole.

U.S. Pat. No. 4,415,547 to Yu et al, discloses sustained release pharmaceutical tablets consisting essentially of drug pellets encapsulated with a water soluble film-forming substance and a water-insoluble film-forming substance. The materials are blended and compressed into tablet form with a compressible tableting mixture.

U.S. Pat. No. 5,059,416 to Cherukuri et al, discloses a process for preparing a zinc compound delivery system comprised of a zinc core material coated with a first hydrophilic coating comprising a hydrocolloid material and a second hydrophobic coating selected from the group consisting of fats, waxes and mixtures thereof. The delivery system masks the bitter flavor characteristic of zinc compounds.

U.S. Pat. No. 4,597,970 to Sharma et al, discloses a delivery system capable of effecting a controlled release of core material comprising: (A) at least one natural or artificial sweet material; and (B) a hydrophobic matrix consisting essentially of (i) lecithin; and (ii) an edible material having a melting point in the range of about 25° C. to about 100° C. selected from the group consisting of (a) fatty acids having an iodine value of about 1 to about 10, (b) natural waxes, (c) synthetic waxes and (d) mixtures thereof; and (iii) at least one glyceride.

Unlike the prior art, the present invention is directed to the discovery of a matrix system that can be used to coat the active component and which achieves a good balance between tastemasking and control of bioavailability of both water-soluble and insoluble active components.

SUMMARY OF THE INVENTION

This invention relates to a substantially tasteless pharmaceutical delivery system, comprising: (a) an active material and (b) a spatially oriented matrix comprising (i) a major amount of a wax core material having a melting point within the range of about 50° C. and about 200° C.; and (ii) a minor amount of a hydrophobic polymer material.

An alternative embodiment involves use of an active material which is a drug selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof disbursed within a matrix comprising a wax core material and a hydrophobic polymer material.

A further embodiment of the invention involves a process for preparing a substantially tasteless pharmaceutical delivery system, comprising melting and blending a major amount of a wax core material and a minor amount of a hydrophobic polymer material at a temperature from about 50° C. to about 200° C. to form a matrix; blending the matrix to form a homogenous mixture of components; adding the active material to the matrix, wherein the temperature of the matrix is maintained below the decomposition temperature of the active material; uniformly dispersing the active material within the matrix to obtain of smooth suspension; and solidifying the mass to form particles of the substantially tasteless pharmaceutical delivery system.

DETAILED DESCRIPTION OF THE INVENTION

The present invention involves the preparation of a tastemasked system by casting or spin congealing melt dispersions and/or solutions of drug or other active material in a molten blend of materials. In this manner a substantially

tasteless pharmaceutical delivery system is formed which comprises: (a) an active material; and (b) a spatially oriented matrix comprising (i) a major amount of wax core material having a melting point within the range of about 50° C. and about 200° C.; and (ii) a minor amount of a hydrophobic polymer material.

The active(s) or drug(s) may be described as a single drug entity or a combination of entities. A drug with high water-solubility is expected to produce immediate release systems, whereas a drug with low water-solubility may produce a controlled or delayed release system. However, controlled or delayed release systems may result when using drugs with high water-solubility. The term "drug" includes without limitations, medicaments, vitamins, mineral supplements and other chemical or biological substances intended for use in the treatment prevention, diagnosis, cure or mitigation of disease or illness, or substances which affect the structure or function of the body.

Suitable categories of drugs that may be employed in the instant aggregate may vary widely and generally represent any stable drug combination. Illustrative categories and specific examples include: (a) antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride; (b) antihistamines, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate; (c) decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ephedrine; (d) various alkaloids, such as codeine phosphate, codeine sulfate and morphine; (e) mineral supplements such as potassium chloride, zinc chloride and calcium carbonates, magnesium oxide and other alkali metal and alkaline earth metal salts; (f) laxatives, vitamins and antacids; (g) ion exchange resins such as cholestyramine; (h) anti-cholesterolemic and anti-lipid agents; (i) antiarrhythmics such as N-acetylprocainamide; (j) antipyretics and analgesics such as acetaminophen, aspirin and ibuprofen; (k) appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and (1) expectorants such as guaifenesin.

Additional useful active medicaments include anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodialators, anti-infectives, psychotropics, antimanics, stimulants, laxatives, gastro-intestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-arrythmics, antihypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, anti-psychotics, antitumor drugs, anticoagulants and antithrombotic drugs, hypnotics, sedatives, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants (anti-tussives), mucolytics, anti-uricemic drugs, and the like.

Mixtures of the drugs and medicaments may also be used.

Particular unpleasant tasting drugs include pyridonecarboxylic acid antibacterial agents whose degree of unpleasantness is said to be strongest, such as 5-amino-1-cyclopropyl- 6,8-difluoro-7-(cis-3,5-dimethyl-1-piperazinyl)- 1,4-dihydro-4-(oxoquinoline-3-carboxylic acid, Enoxacin, Pipemidic acid, Ciprofloxacin, Ofloxacin, and Pefloxacin; antiepileptic drugs such as Zonisamide; macrolide antibiotics such as Erythromycin; beta-lactam antibiotics such as penicillins or cephalosporins; psychotropic drugs such as Chlorpromazine; drugs such as Sulpyrine; and antiulcer drugs such as Cimetidine. Suitable among these drugs are pyridonecarboxylic acid antibacterial agents, especially 5-amino-1-cyclopropyl-6,8-difluoro-7-(cis- 3,5-dimethyl-1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid or Enoxacin, because the preparations of this invention have an excellent effect of masking the unpleasant taste. An exemplary decongestant is pseudoephedrine hydrochloride and mineral would be zinc salts.

The drugs were used in amounts that are therapeutically effective. While the effective amount of a drug will depend on the drug used, amounts of drug from about 5% to about 65% have been easily incorporated into the present matrix while achieving bitter taste masking. Amounts above about 65% may result in the loss of tasteless properties.

As indicated above, the tastemasked systems may be formed in a variety of ways, such as casting or spray congealing melt dispersions and/or solutions of active in a molten blend of materials. In this way, the tastemasked systems are dispersed in melt hardening and body fluid dispersable/dissolvable materials to form a suspension. The suspensions may then be further formulated with excipient materials to form the final dosage form or material to be used in the final dosage form.

The spatially oriented matrix used to mask the unpleasant taste of the active material must contain two separate components; a major amount of a wax core material having a melting point within the range of about 50° C. to about 200° C. and a separate minor amount of a hydrophobic polymer material.

The wax core material is present in the matrix in amounts of about 10% to about 95% and preferably about 15% to about 85% by weight of the matrix. The wax core material is always present in amounts greater than the hydrophobic polymer and thus has been described as being present in a major amount. The term "core" is used herein to define the substance forming the backbone component of the matrix.

The wax core material may be chosen from a wide variety of materials. Particularly preferred materials are selected from the group consisting of long chain fatty hydrocarbons, esters, acids and alcohols of straight or branched chain alkyls having from 12 to 32 carbon atoms.

Particularly preferred materials are selected from animal waxes, vegetable waxes, petroleum waxes, synthetic waxes, and mixtures thereof and include without limitation beeswax, lanolin, stearic acid, candelilla wax, carnauba wax, microcrystalline wax, carbowax and mixtures thereof.

The hydrophobic polymer material is present in the matrix in amounts of about 1% to about 50% and preferably about 3% to about 10% by weight of the matrix. As discussed above, the hydrophobic polymer is present in amounts less than the wax core material. The hydrophobic polymer material is preferably a material that has some solubility in the wax core material and is selected from a variety of natural polymers or derivative thereof as well as synthetic polymers. Exemplary natural polymers include cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, ethyl cellulose, zein, pharmaceutical glaze, shellac, chitan, pectin, polypeptides, acid and base addition salts thereof, and mixtures thereof. Exemplary synthetic polymers include polyacrylates, polymethacrylates, polyvinyl acetate, acetate phthalate, polyanhydrides, poly(2-hydroxyethyl methacrylate), polyvinylalcohols, polydimethyl siloxone, silicone elastomers, acid and base addition salts thereof, and mixtures thereof. The term "hydrophobic polymer" as used herein refers to polymeric materials that are typically antagonistic to water, i.e., incapable of dissolving in water

even though they may have regional areas in the molecule that have some hydrophilic properties.

In addition to the wax core material and the hydrophobic polymer material, the matrix may contain additional ingredients herein referred to as excipients or additives. Exemplary excipients include, but are not limited to sweetening agents, colorants, surfactants, flavors, fragrances, pH modifiers, bulking agents, and mixtures thereof which components may be used in an amount of about 0.01% to about 75% by weight of the matrix.

When preparing the matrix, it is important to consider the physical properties of the materials used. Those compounds which exhibit an elasticity or plastic property appear to be best suited for the matrix, as opposed to very hard waxes such as carnauba. Through a matrix composed completely of a hard natural wax does not give the desired effect, hard natural wax can be used in a portion of the matrix. Portions of the matrix may contain common triglyceride fats and or waxes of a brittle nature such as carnauba to modify physical characteristics of the final matrix. This modification may be necessary to satisfy processing criteria at the congealing phase of the product, or further processing such as tableting or dry powder packaging.

It is believed that dissolution of appropriate polymers in the wax melt formulations modifies the Gibbs Free Energy of the resulting spatially oriented continuum (SOC). The presence of the hydrophobic polymer aids the hydrophobization of the active material immersed in the melt wax by virtue of selective adsorption onto active surface centers.

Spreading of a SOC on a solid substrate is described by the "spreading coefficient" which is a function of the changes of the chemical potentials of the materials involved. Particularly, low-melting solids, such as organic polymers, waxes, and covalent compounds, in general have surface free energies ranging from 100 to 25 ergs/cm^2. In the case of a solid substrate, the surface and interfacial tensions are measured individually by contact angle of the wetting liquid on the substrate. For spontaneous wetting this angle should be zero. For the system which involves immersional wetting, the contact angle requirement is less stringent and only requires the contact angle to be less than 90 degrees for immersional wetting to be spontanegus.

Several variables may effect the release characteristics of the dispersed phase and include, particle size, particle size distribution and distribution of the active, material concentration, cooling or solidification rates and conditions, and final form of the system, such as cast sheets or congealed particles.

It is believed that the release mechanism of active components may be a combination of several phenomena. Enzymatic degradation of the matrix, diffusion of the drug through the SOC, competitive adsorption, desorption of hydrophobic components from hydrophilic surface centers, convection of the drug through mesopores and macropores, diffusion of the external medium into the matrix by way of solubility or capillary action through porous structures created by the addition of hydrophilic polymers or water-soluble solids, diffusion from the surface of a capsule due to incomplete coating of drug particles, cracks caused for instance by the difference in thermal expansion between coated drug and matrix, disintegration or erosion of the SOC.

The tasteless pharmaceutical delivery system is prepared by first selecting the matrix components for the particular active ingredient and end use of material. The wax component is melted, and the selected hydrophobic polymer material dissolved in the melt. The composition of hydrophobic polymer material in this system ranges from about 1% to about 50% relative to the selected wax, with preferred levels from about 3% to about 10% by weight of the matrix. Temperatures are adjusted to facilitate the solution, ranging from 50° C. to 200° C., with preferred temperatures from 70° C. to 160° C. Once the hydrophobic polymer material is incorporated satisfactorily, additional wax components can be added and processed to obtain a uniformblend. The composition of additional wax components may varywidely from 0% to 99% relative to the total content of the final matrix but are preferably from 4% to 75% by weight of the matrix. The active ingredients are then added to form the final mixture, which can also be obtained by adding the active ingredients prior to the additional matrix components. It may be necessary at this point to adjust the temperature of the melt to prevent decomposition of the active ingredient.

Slurring of the active ingredient can initially be done by simple stirring. However, in most cases it is necessary to use a high speed mixer and sometimes a colloid mill to obtain a smooth suspension, free of agglomerates. Once a smooth suspension is obtained, it may be necessary to readjust the temperature to provide the proper rheological characteristics for processing, preferably from about 70° C. to about 110° C. The slurry is congealed using technology well knownto the ordinary skilled artisan or rapidly cooled and ground, if required. The final activity of the resultant product may range from 1% to 60%, preferably from 10% to 50%. These final systems and combination of materials result in product with unanticipated benefits of tastemasking noxious drug substances.

In a particularly preferred procedure, a process for preparing a substantially tasteless pharmaceutical delivery system comprises: a) melting a wax core material and a hydrophobic polymer material at a temperature from about 50° C. to about 200° C. to form a matrix; b) blending the matrix to form a homogenous mixture of components; c) adding the active material to the matrix, wherein the temperature of the matrix is maintained below the decomposition temperature of the active material; d) uniformly dispersing the active material within the matrix to obtain of smooth suspension; e) solidifying the mass while spray or spin congealing the molten material to form particles of the substantially tasteless pharmaceutical delivery system. The particles obtained are usually between about 10 μ to about 400 μ in size. Larger particles may be ground if required for further processing.

Since tastemasking is a key feature of the invention, the use of the invention in sublingual or buccal systems is contemplated, but not generally preferred. However, other systems in which the product would not normally be expected to be retained in the mouth for significant amounts of time are contemplated. Thus, chewable and/or dissolvable dosage forms would be particularly improved with this technology. Further, fluid oral dosage forms would also be particularly improved with this technology.

One dosage form contemplated, involves the use of gelatin or other plastic matrix(es) in a capsule containing the inventive aggregate and/or materials containing the inventive delivery system in combination with one or more conventional excipients.

The term "excipients" as used herein mean substances and materials generally used in the drug or food industry which do not alter the character and function of the active component of the aggregate.

Flavors which may optionally be added to the delivery system are those well known in the confectionery art. For

example, synthetic flavor oils, and/or oils from plants, leaves, flowers, fruits and so forth, and combinations thereof are useful.

Representative flavor oils include spearmint oil, peppermint oil, cinnamon oil, and oil of wintergreen (methylsalicylate). Also useful are artificial, natural or synthetic fruit flavors such as citrus oils including lemon, orange, grape, lime, and grapefruit, and fruit essences including apple, strawberry, cherry, pineapple and so forth.

The amount of flavoring agent employed is normally a matter of preference subject to such factors as flavor type, base type and strength desired. In general, amounts of about 0.05% to about 5.0% by weight of the final product are useful with amounts of about 0.3 % to about 1.5% being preferred and about 0.8% to about 1.2% being most preferred.

The matrix may contain a sweetening agent. Sweetening agents may be selected from a wide range of materials such as water-soluble sweetening agents, water-soluble artificial sweeteners, and dipeptide based sweeteners, including mixtures thereof. Without being limited to particular sweeteners, representative illustrations encompass:

A. Water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, sugar, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof.

B. Water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, acesulfam-K and the like, and the free acid form of saccharin.

C. Dipeptide based sweeteners such as L-aspartyl L-phenylalanine methyl ester and materials described in U.S. Pat. No. 3,492,131 and the like.

While delivery systems based on the instant invention are generally solid or semi-solid, it is contemplated that they may be employed, with or without the conventional supplemental agents, as principal components of systems to be dissolved or dispersed in water or other ingestible liquids for ingestion in a drinkable form.

The excipients are added to the matrix anytime during processing. It should be recognized that certain excipients should be added prior to, during or after the active material is blended into the matrix in order to achieve uniform distinction of the ingredients. Preferably, excipients in liquid form are added before the active material whereas powdered excipients may be added before or after the active material is added.

The following examples are illustrative of preferred embodiments of the invention and are not to be construed as limiting the invention thereto. All percentages are based on the percent by weight of the matrix unless otherwise indicated and all totals equal 100% by weight.

EXAMPLE 1

This example demonstrates the production of tasteless granules of pseudoephedrine hydrochloride.

To a suspension of beeswax (81.6% w/w) and ethyl cellulose (10 cps, 3% w/w) which was melted at a temperature of 70°–80° C. and blended to form a homogenous mixture was added pseudoephedrine hydrochloride (15.4% w/w). The suspension was blended for 10–15 minutes, and cooled in air while spin congealing to form a solid particulate material. Particles of spin congealed material when chewed by a panel comprising at least five members, the product did not exhibit any bitter taste.

EXAMPLE 2

This example demonstrates the production of various forms of active material.

To a molten blend of beeswax, carnauba wax or Witepsol® (a triglyceride fat of Hüls America Inc.) each at (82% w/w) and ethyl cellulose (10 cps, 3% w/w) which were melted, blended and maintained at a temperature of 120° C. was added pseudoephedrine hydrochloride (15% w/w).

The slabs produced that were based on carnauba wax and Witepsol® when chewed exhibited a bitter taste, while granules and slabs based on beeswax when chewed did not exhibit a bitter taste. Therefore, the mechanism of congealing and geometry of the system influence the degree of taste.

COMPARATIVE EXAMPLE A

This example demonstrates the production of comparative granules with beeswax alone.

The procedure of Example 1 was repeated with melted beeswax (85% w/w) blended with pseudoephedrine hydrochloride (15% w/w).

The granules when chewed exhibited a bitter taste. Therefore the presence of the hydrophobic polymer material is required to create a tastemasked system.

EXAMPLE 3

This example demonstrates the preparation of a delivery system with a hydrophobic polymer material.

The procedure of Example 1 was repeated using a blend of beeswax (82% w/w) with ethyl cellulose (10 cps 3% w/w) or a methylacrylate polymer (Eudragit® RS100 by Rohm Pharma) (3% w/w). The material was cast into a block and taste tested. Neither of the systems exhibited a bitter taste when tested. It is therefore concluded that the hydrophobic polymer material properties such as hydrophobicity and miscibility in the core wax material influence the tastemasking properties of the matrix.

EXAMPLE 4

The procedure of Example 1 was repeated to prepare granulars from 6-methoxy erythromycin A (8%, 16% and 25% w/w respectively) suspended in a blend of ethyl cellulose, Ethocel (10 cps., 3% w/w), in beeswax (89% and 72% w/w, respectively). The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to alternative drug forms.

EXAMPLE 5

The procedure of Example 1 was repeated to prepare: granulars from acetaminophen (35.38% w/w), pseudoephedrine hydrochloride (3.32% w/w), chloropheniramine maleate (0.21% w/w) and dextromethorphan (1.10% w/w) suspended in a blend of ethyl cellulose, Ethocel (10 cps, 3.00% w/w), beeswax (17.00% w/w) , sorbitan monoloeate, 3.00% w/w and mono- and di-glycerides, 36.99% w/w. The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to wax mixtures.

EXAMPLE 6

The procedure of Example 1 was repeated to prepare granulars from ascorbic acid (19.84% w/w) and folic acid (0.16% w/w) suspended in a blend of ethyl cellulose, (10 cps., 4.00% w/w) sorbitan monoloeate (4.00% w/w), hydrogenated vegetable oil, (8.00% w/w) and candelilla wax (64.00% w/w). The particle granulars when chewed did not exhibit a sour taste. Therefore, these systems are applicable to wax mixtures and other wax materials.

EXAMPLE 7

The procedure of Example 1 was repeated to prepare granulars from ibuprofen (40.00% w/w) suspended in a blend of ethyl cellulose, (10 cps., 3.00%w/w), sorbitan monoleate (3.00% w/w), beeswax (12.25% w/w) carnauba wax (6.00% w/w) and mono- and di- glycerides (35.75% w/w). The granulars when chewed did not exhibit a bitter taste. Therefore, these systems are applicable to wax mixtures.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

What is claimed is:

1. A substantially tasteless pharmaceutical delivery system, which comprises a molten blend of:

a) an active material; and

b) a spatially oriented matrix comprising:

(i) a major amount of about 10% to about 95% by weight of the matrix of a wax core material having a melting point within the range of about 50° C. and about 200° C.; and

(ii) a minor amount of about 1% to about 50% by weight of the matrix of a hydrophobic polymer material selected from the group consisting of natural polymers and synthetic polymers,

wherein the total amount of the matrix is equal to 100%.

2. The delivery system of claim 1, wherein the active material is a pharmaceutical drug.

3. The delivery system of claim 1, wherein the active material is selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins,-metal salts, and mixtures thereof.

4. The delivery system of claim 1, wherein the wax core material is selected from the group consisting of long chain fatty hydrocarbons, esters, acids and alcohols of straight or branched chain alkyls having from 12 to 32 carbon atoms.

5. The delivery system of claim 4, wherein the wax core material is selected from the group consisting of animal waxes, vegetable waxes, petroleum waxes, synthetic waxes, and mixtures thereof.

6. The delivery system of claim 5, wherein the wax core material is selected from the group consisting of beeswax, lanolin, stearic acid, candelilla wax, carnauba wax, microcrystalline wax, carbowax and mixtures thereof.

7. The delivery system of claim 1, wherein the hydrophobic polymer material is present in an amount of about 1% to about 50% by weight of the matrix.

8. The delivery system of claim 1, wherein the hydrophobic polymer material is present in an amount of about 3% to about 10% by weight of the matrix.

9. The delivery system of claim 1, wherein the natural polymer is selected from the group consisting of cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, ethyl cellulose, zein, pharmaceutical glaze, shellac, chitan, pectin, polypeptides, acid and base addition salts thereof, and mixtures thereof.

10. The delivery system of claim 1, wherein the synthetic polymer-is selected from the group consisting of polyacrylates, polymethacrylates, polyvinyl acetate, polyvinyl acetate phthalate, polyanhydrides, poly(2-hydroxyethyl methacrylate), polyvinylalcohols, polydimethyl siloxone, silicone elastomers, acid and base addition salts thereof, and mixtures thereof.

11. The delivery system of claim 1, wherein the matrix includes an excipient.

12. The delivery system of claim 1, wherein the excipient is present in the matrix in an amount of about 0.01% to about 75% by weight of the matrix.

13. The delivery system of claim 1, wherein the excipient is selected from the group consisting of sweetening agents, colorants, surfactants, flavors, fragrances, pH modifiers, bulking agents, and mixtures thereof.

14. A substantially tasteless pharmaceutical delivery system which comprises:

a) an effective amount of an active material selected from the group consisting of analgesics, anti-inflammatories, antihistamines, antitussives, expectorants, decongestants, narcotics, antibiotics, bronchodilators, cardiovasculars, central nervous system drugs, minerals, vitamins, metal salts, and mixtures thereof; and

b) a spatially oriented matrix comprising:

(i) from about 10% to about 95% of a wax core material having a melting point within the range of about 50° C. and about 200° C.; and

(ii) from about 1% to about 50% of a hydrophobic polymer material; and remaining amount up to 100% of an additional excipient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,494,681
DATED : February 27, 1996
INVENTOR(S) : CUCA et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Claim 3, column 9, line 48, change "vitamins,-metal" to —vitamins, metal—;

Claim 10, column 10, line 21, change "polymer-is" to —polymer is—;

column 5, line 42, change "spontanegus" to —spontaneous—; and

column 6, line 9, change "uniformblend" to —uniform blend—.

Signed and Sealed this
Eleventh Day of June, 1996

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks